Remote ischaemic conditioning on recipients of deceased renal transplants, effect on immediate and extended kidney graft function

Krogstrup, Nicoline V; Oltean, Mihai; Bibby, Bo M; Nieuwenhuijs-Moeke, Gertrude J; Dor, Frank J M F; Birn, Henrik; Jespersen, Bente

Published in:
BMJ Open

DOI:
10.1136/bmjopen-2015-007941

Publication date:
2015

BMJ Open

Remote ischaemic conditioning on recipients of deceased renal transplants, effect on immediate and extended kidney graft function: a multicentre, randomised controlled trial protocol (CONTEXT)

Nicoline V Krogstrup,[1,2] Mihai Oltean,[3] Bo M Bibby,[4] Gertrude J Nieuwenhuijs-Moeke,[5] Frank J M F Dor,[6] Henrik Birn,[1,7] Bente Jespersen[1,2]

To cite: Krogstrup NV, Oltean M, Bibby BM, *et al*. Remote ischaemic conditioning on recipients of deceased renal transplants, effect on immediate and extended kidney graft function: a multicentre, randomised controlled trial protocol (CONTEXT). *BMJ Open* 2015;**5**:e007941. doi:10.1136/bmjopen-2015-007941

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-007941).

Received 11 February 2015
Revised 29 May 2015
Accepted 16 June 2015

For numbered affiliations see end of article.

Correspondence to
Nicoline V Krogstrup; nicoline.v.krogstrup@clin.au.dk

ABSTRACT

Introduction: Delayed graft function due to ischaemia-reperfusion injury is a frequent complication in deceased donor renal transplantation. Experimental evidence indicates that remote ischaemic conditioning (RIC) provides systemic protection against ischaemia-reperfusion injury in various tissues.

Methods and analysis: 'Remote ischaemic conditioning in renal transplantation—effect on immediate and extended kidney graft function' (the CONTEXT study) is an investigator initiated, multicentre, randomised controlled trial investigating whether RIC of the leg of the recipient improves short and long-term graft function following deceased donor kidney transplantation. The study will include 200 kidney transplant recipients of organ donation after brain death and 20 kidney transplant recipients of organ donation after circulatory death. Participants are randomised in a 1:1 design to RIC or sham-RIC (control). RIC consists of four cycles of 5 min occlusion of the thigh by a tourniquet inflated to 250 mm Hg, separated by 5 min of deflation. Primary end point is the time to a 50% reduction from the baseline plasma creatinine, estimated from the changes of plasma creatinine values 30 days post-transplant or 30 days after the last performed dialysis post-transplant. Secondary end points are: need of dialysis post-transplant, measured and estimated-glomerular filtration rate (GFR) at 3 and 12 months after transplantation, patient and renal graft survival, number of rejection episodes in the first year, and changes in biomarkers of acute kidney injury and inflammation in plasma, urine and graft tissue.

Ethics and dissemination: The study is approved by the local ethical committees and national data security agencies. Results are expected to be published in 2016.

Trial registration number: NCT01395719.

INTRODUCTION

Delayed graft function (DGF) following deceased donor kidney transplantation may lead to need of dialysis, increased incidence of post-transplant complications and prolonged hospitalisation.[1–3] In transplantation with kidneys from brain death donors (DBD), DGF is associated with an increased risk of acute rejection episodes, and impaired graft function and survival.[1 2 4–6] DGF is closely related to ischaemia-reperfusion injury (IRI) and complicates 20–45% of transplantations from DBD,[5] and 50–75% of transplantations with kidneys from circulatory death donors (DCD).[7–9] The incidence of DGF and also primary non-function might increase with higher acceptance of extended criteria donors and thus lower organ quality, necessitated by the persisting organ shortage. Remote ischaemic conditioning (RIC) has been shown to protect against IRI in various tissues.[10 11] In the heart, this was shown in animal studies of myocardial injury,[12 13] as well as in clinical trials after acute myocardial infarction (AMI)[14 15] and following heart surgery in children.[16] Lately, RIC has been shown to affect long-term clinical outcomes positively, including a reduction in all-cause mortality after AMI and coronary artery bypass surgery.[17 18] Clinical trials have also shown that RIC protects against acute kidney injury (AKI), for example, after cardiac surgery[19] or interrupted renal blood supply during elective aortic surgery;[20] however, this finding has not been confirmed in all studies.[21–23] It has been suggested that RIC may protect against DGF after kidney

transplantation.[24–26] In a porcine DBD transplantation model, we have shown that RIC on the recipient animal was associated with higher glomerular filtration rate (GFR) and plasma perfusion of the transplanted kidney within the first 10 h of reperfusion.[27] So far, two clinical trials investigating the effect of RIC in kidney transplantation have been published: a small trial (published as a letter to editor), using RIC in living donor kidney transplantation, studied three groups with 20 kidney-transplanted patients in each, exposed to either donor RIC, recipient RIC or nothing (control group).[28] No effect of RIC was observed on the incidence of DGF, plasma creatinine (p-cr) levels, urinary output, hospitalisation days and costs or various biomarkers in plasma and urine. The negative finding, however, was limited by the low sample size and the known low frequency of DGF from live donation. Another small trial applying RIC to DCD recipients (n=48), showed that RIC was associated with an increase in early estimated-GFR (eGFR) and a decrease in urine concentration of the renal injury marker neutrophil gelatinase-associated lipocalin (NGAL).[29]

The CONTEXT study investigates the effect of RIC in recipients of kidneys from deceased donors, including mainly DBD, as well as DCD, in a block randomised design. To our knowledge, three other randomised clinical trials are presently investigating the effects of different RIC strategies in kidney transplantation (the REPAIR trial (UK and the Netherlands),[30] the RIPNOD study (US)[31] and 'Remote Post-Conditioning (RPC) in renal transplantation' (UK)[32]). The protocols of these studies differ in several ways from the CONTEXT study, both with respect to RIC procedure and the patient study groups.

In addition to studying the effect of RIC on renal function and clinical outcome, the newest concepts and technologies will be used to identify various ischaemic, inflammatory and immunological biomarkers and mediators in renal tissue, urine and blood expected to be associated with ischaemia-reperfusion injury and RIC. Obtained knowledge in this field will potentially have high impact in prevention of AKI in transplantation and other clinical settings.

METHODS AND ANALYSIS

Study type

An investigator initiated multicentre, randomised, controlled and prospective clinical trial. The study is blinded to the patient, surgeons and treating physicians.

Study population

Patients above 18 years of age receiving a DBD (n=200) or DCD (n=20) renal transplant at Aarhus University Hospital, Aarhus, Denmark; Sahlgrenska University Hospital, Gothenburg, Sweden; University Medical Center Groningen, Groningen, and Erasmus MC, University Medical Center, Rotterdam, the Netherlands. Kidney transplantation from DCD is carried out only in the latter two centres.

The Dutch centres will be starting inclusion after the Scandinavian centres and thus, only a minor group of DCD recipients will be included in the present study, which depending on the results, can be expanded.

Donor and recipient selection follow the regional allocation programmes, Scandiatransplant (Aarhus and Gothenburg) and Eurotransplant (Groningen and Rotterdam). Final recipient selection in Aarhus and Gothenburg is based on local guidelines regarding immunological match and specified donor/recipient characteristics independent of the CONTEXT protocol. See table 1 for study inclusion and exclusion criteria. Treatment before and during the operation is specified below. Concomitant care and interventions during the study follow-up period are carried out according to local standards. The patients cannot participate in other randomised intervention trials during the follow-up period.

Randomisation

Patients are informed and enrolled into the study by the surgeon or physician on duty. Randomisation, intervention and handling of study samples is carried out by a trained study crew member attending the operation who is either a medical student, a laboratory technician or the local, principal investigator (who is not involved in the patient care). Patients are randomised in a 1:1 fashion to either RIC or sham-RIC (control group) stratified by centre and donor type, using an online block randomisation programme. When both recipients of the kidneys from the same donor are included in the study, they are randomised within kidney pairs (figure 1) and stratified by operation sequence, in order to distribute cold ischaemia time evenly.

Figure 2 shows the sampling and study timeline.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
▶ Deceased donor kidney transplantation candidate	▶ AV-fistula in the leg of planned RIC (opposite to the side of graft implantation)
▶ Aged 18 years or older	▶ Increased risk of complications from RIC due to pre-existing lower limb ischaemia (as determined by the investigator)
▶ Informed consent	▶ Unable to deliver informed consent
	▶ Double kidney transplant recipient

AV, arteriovenous; RIC, remote ischaemic conditioning.

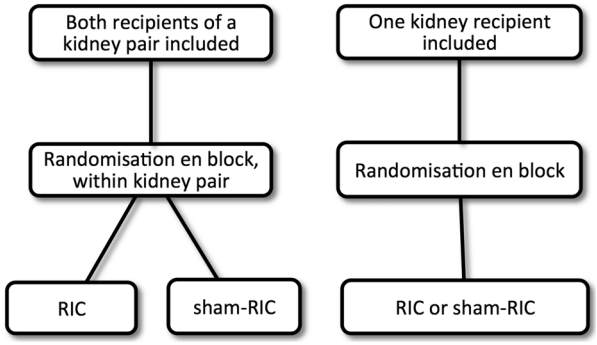

Figure 1 Randomisation algorithm (RIC or sham-RIC, 1:1) by the online block randomisation programme, stratified by centre and donor type. When both recipients of a kidney pair are included, randomisation is also stratified by operation order. RIC, remote ischaemic conditioning

RIC or sham

In the operation theatre, prior to the start of surgery, an appropriately sized tourniquet is placed on the thigh of all patients opposite to the side of planned graft implantation. The RIC/sham procedure is initiated approximately 40 min prior to the expected time of graft reperfusion, usually shortly after the skin incision. If the patient is randomised to RIC, the blood supply to the lower limb is occluded by inflation of the tourniquet to 250 mm Hg in four cycles of 5 min, separated by 5 min of deflation to allow free blood flow. The tourniquet remains deflated in the control group, but the activity of the attending staff is as in the intervention group. The randomisation is blinded to the surgeons and anaesthesiologist. RIC is terminated just prior to graft reperfusion even if the four cycles are not fully completed.

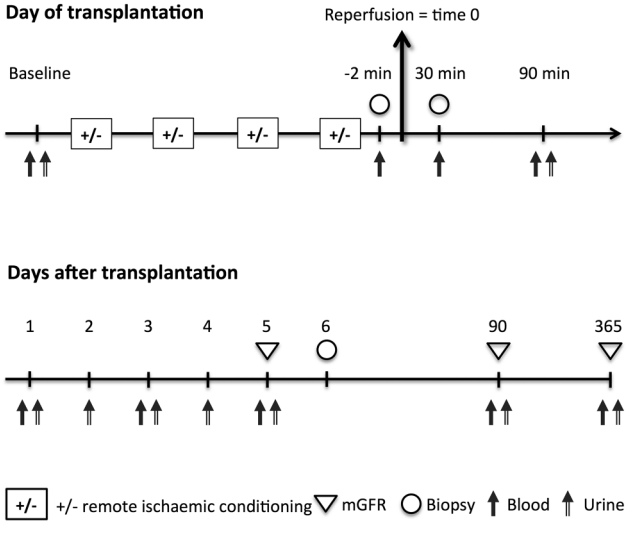

Figure 2 Timing of intervention (± remote ischaemic conditioning), samples, measurements and follow- up; mGFR, measured glomerular filtration rate.

Anaesthesia and transplantation procedures

Anaesthesia is induced with propofol and fentanyl/remifentanil. To facilitate tracheal intubation and to optimise ventilation and surgical conditions, cisatracurium is used as a muscle relaxant. Anaesthesia is maintained with sevoflurane and analgesia with fentanyl or remifentanil according to local protocol. Volatile anaesthetic agents were chosen because of their possible amplifying effect on RIC.[33–35] The surgical procedure follows local standards. Fluid replacement therapy during the procedure is based on crystalloids, either normal saline or Ringers Lactate and human albumin. No synthetic colloids are used. Hypotension during surgery is managed at the discretion of the attending anaesthesiologist. Before reperfusion, 200–350 mL Mannitol 15% is given according to local protocol.

Immunosuppression

The immunosuppressive regimen is based on induction with intravenous basiliximab and methylprednisolone or corresponding oral doses of prednisolone, followed by oral tacrolimus, mycophenolate mofetil and prednisolone (starting at 20 mg/day and slowly tapered to 5 mg/day).

Primary end point

The primary end point is the estimated time to a 50% decrease in plasma-creatinine (p-cr). Baseline p-cr is measured approximately 1 h prior to the graft reperfusion. P-cr is then measured at least twice daily day 1–4, once daily day 5–7 and two times weekly until 30 days after transplantation. For patients requiring temporary dialysis post-transplant, p-cr is measured continuously until 30 days after the last dialysis. All p-cr values will be noted with date and time of the sample, and the time (hours) since reperfusion will be calculated. The observed, time dependent changes in p-cr are modulated for each patient by an exponential, logistic or a linear model; by using this model, the p-cr at reperfusion (time 0) and the time to a 50% decrease of this value is estimated. This primary end point will allow the inclusion in the analysis of all patients who acquire kidney graft function with a GFR greater than about 20 mL/min, including patients requiring initial, temporary dialysis.

Secondary end points

Need of dialysis post-transplant. GFR measured by ^{51}Cr-EDTA or iodothalamate plasma clearance at day 5, and 3 and 12 months post-transplant. Number of acute rejection episodes the first year post-transplant. Patient and renal graft survival. Absolute levels of and changes in expression of renal tissue markers at day 6 post-transplant compared to time zero. Metabolomics and proteomics analyses on paired kidney biopsies on day 6. Plasma concentration and urinary excretion of markers and mediators of renal injury and RIC based on various assays, including ELISA and expression array studies. Among others, the AKI marker NGAL[36 37] will be measured in urine and plasma, as well as the markers liver

fatty acid-binding protein,[38] cystatin C[36] and YKL40[39] (only in urine). Further analyses are still to be decided.

Statistics

The primary analyses of the outcome parameters will be based on the results of recipients of both donor groups; secondary analyses will investigate the results divided into donor subgroups.

Outcomes will be presented as means with SDs and groups will be compared using Student t test if data are normally distributed, and if not compared by the Wilcoxon two-sample rank sum test. Binary outcomes will be analysed using χ^2 test or Fisher's exact test.

Repeated measurements will be analysed using a repeated measurement analysis of variance. A linear mixed effects model will be applied with treatment and time as fixed effects, and with recipient and donor as random effects.

The p value <0.05 will be considered statistically significant.

The sample size was determined based on estimates from a pilot study including 62 kidneys from 54 DBD. The geometric mean time to reach 50% of the initial p-cr level was 57.04 h and the geometric SD was 2.44 h within donors and 2.33 h between donors. The sample size was calculated under the assumption that all new donors would contribute two kidneys each, which would be randomised to either RIC or sham-RIC (control). The number of donors should be large enough to determine a statistical significant 30% decrease in the time to reach a 50% p-cr reduction in the RIC group compared to the sham-RIC group. The test for no treatment effect was based on the likelihood ratio test statistic from a linear mixed effects analysis, with treatment as fixed effect and donor as a random effect. The significance level was set to 0.05 and the power to 0.80. The result of the sample size calculation was that a total of 100 donors are needed, thus 200 recipients. With the inclusion of the Dutch centres we have decided to include 20 recipients extra, as it is anticipated that not all donors will contribute two kidneys. The primary analysis will be on all recipients, with subanalyses on DBD and DCD.

Study group

The study group is composed of the trial sponsor in Aarhus (BJ, HB and NVK, the latter principal investigator) and local investigator in Gothenburg MO, local investigator in Groningen GJNM and local investigator in Rotterdam FJMFD. Each investigator is locally in charge of the execution of the study, and gathering of samples and data. Trial sponsor is in charge of data entry, storage, statistical analyses and writing. Legal study agreements are made between trial sponsor and each additional study site regarding performance of the study, timelines and recruitment, reporting, data management, confidentiality and intellectual property, publication, liability and indemnification, termination, law and venue.

ETHICS AND DISSEMINATION

Ethical and safety considerations

The study protocol, including consent form and participant information, is approved by the national agencies in Denmark, Sweden and the Netherlands, including the local ethical committees (Denmark: 31894 November 2011, Netherlands 2013/141) and the Data protection agencies (Denmark: J.nr. 2011-41-6477). All minor and major amendments to the protocol need approval by the ethical committees. A data monitoring committee was not required.

The tourniquet used is designed to create bloodless operation fields and is often used in orthopaedic operations. With prolonged usage (>1 h), skin damages can occur if the skin is folded under a badly applied tourniquet. This is not likely to occur using short, repeated RIC interrupted by free flow of blood, as described. To our knowledge, no adverse events have been reported by other clinical trials applying RIC on a limb with a tourniquet. A serious adverse event possibly related to the ischaemic insult of the leg is believed to have happened within the first week after the operation. According to the seriousness of the event, the intervention of the patient can be unblinded after internal discussion in the study group.

The anaesthetised patient will experience no discomfort.

The study is conducted in accordance with the ethical principles of the Declaration of Helsinki and the Declaration of Istanbul. Authorship will be decided as described in the legal study agreements between trial sponsor and additional study sites, and according to the Vancouver guidelines.

Dissemination plan

Results will be presented at national and international meetings and in the media, and published in international peer-reviewed medical journals. First results are expected in 2016.

Author affiliations
[1]Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark
[2]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark
[3]The Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden
[4]Department of Biostatistics, Aarhus, Denmark
[5]Department of Anaesthesiology, University Medical Center Groningen, Groningen, The Netherlands
[6]Division of HPB & Transplant Surgery, Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[7]Department of Biomedicine, Aarhus University, Aarhus, Denmark

Contributors The original idea and study protocol was derived from the initiating investigator study group in Aarhus (NVK, BMB, HB and BJ), with assistance from MO. NVK wrote the draft. Revision was performed by the coauthors. BMB was in charge of the statistical content.

Funding The study is supported by the Lundbeck Foundation (grant number R67-A6224), the Danish Council for Independent Research (grant number 1331-00314A), the Novo Nordic Foundation, Nyreforeningen (the Danish kidney patient association), the Danish Society of Nephrology, A.P. Møller og hustru Chastine MC-Kinney Møllers Fond til Almene Formaal, Aarhus University and Aarhus University Hospital.

Competing interests None declared.

Ethics approval The Scientific Ethical Committee Region Midt, Denmark (31894), and the Danish Data Protection Agency (2011-41-6477). In addition, the corresponding local agencies in Sweden and the Netherlands.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Ojo AO, Wolfe RA, Held PJ, *et al*. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 1997;63:968–74.
2. Miglinas M, Supranaviciene L, Mateikaite K, *et al*. Delayed graft function: risk factors and the effects of early function and graft survival. *Transplant Proc* 2013;45:1363–7.
3. Perico N, Cattaneo D, Sayegh MH, *et al*. Delayed graft function in kidney transplantation. *Lancet* 2004;364:1814–27.
4. Nicholson ML, Wheatley TJ, Horsburgh T, *et al*. The relative influence of delayed graft function and acute rejection on renal transplant survival. *Transpl Int* 1996;9:415–19.
5. Yarlagadda SG, Coca SG, Formica RN Jr, *et al*. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2009;24:1039–47.
6. Guimaraes-Souza N, Dalboni MA, Canziani ME, *et al*. Clinical implications of initial renal function after deceased donor transplant. *Transplant Proc* 2010;42:1084–9.
7. Summers DM, Johnson RJ, Allen J, *et al*. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet* 2010;376:1303–11.
8. Snoeijs MG, Winkens B, Heemskerk MB, *et al*. Kidney transplantation from donors after cardiac death: a 25-year experience. *Transplantation* 2010;90:1106–12.
9. Tojimbara T, Fuchinoue S, Iwadoh K, *et al*. Improved outcomes of renal transplantation from cardiac death donors: a 30-year single center experience. *Am J Transplant* 2007;7:609–17.
10. Heusch G, Botker HE, Przyklenk K, *et al*. Remote Ischemic Conditioning. *J Am Coll Cardiol* 2015;65:177–95.
11. Candilio L, Malik A, Hausenloy DJ. Protection of organs other than the heart by remote ischemic conditioning. *J Cardiovasc Med (Hagerstown)* 2013;14:193–205.
12. Shimizu M, Konstantinov IE, Kharbanda RK, *et al*. Effects of intermittent lower limb ischaemia on coronary blood flow and coronary resistance in pigs. *Acta Physiol (Oxf)* 2007;190:103–9.
13. Konstantinov IE, Li J, Cheung MM, *et al*. Remote ischemic preconditioning of the recipient reduces myocardial ischemia-reperfusion injury of the denervated donor heart via a Katp channel-dependent mechanism. *Transplantation* 2005;79:1691–5.
14. Botker HE, Kharbanda R, Schmidt MR, *et al*. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* 2010;375:727–34.
15. Kharbanda RK, Nielsen TT, Redington AN. Translation of remote ischaemic preconditioning into clinical practice. *Lancet* 2009;374:1557–65.
16. Cheung MM, Kharbanda RK, Konstantinov IE, *et al*. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol* 2006;47:2277–82.
17. Sloth AD, Schmidt MR, Munk K, *et al*. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *Eur Heart J* 2014;35:168–75.
18. Thielmann M, Kottenberg E, Kleinbongard P, *et al*. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet* 2013;382:597–604.
19. Zimmerman RF, Ezeanuna PU, Kane JC, *et al*. Ischemic preconditioning at a remote site prevents acute kidney injury in patients following cardiac surgery. *Kidney Int* 2011;80:861–7.
20. Ali ZA, Callaghan CJ, Lim E, *et al*. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation* 2007;116:I98–105.
21. Pedersen KR, Ravn HB, Povlsen JV, *et al*. Failure of remote ischemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: a randomized single-center study. *J Thorac Cardiovasc Surg* 2012;143:576–83.
22. Choi YS, Shim JK, Kim JC, *et al*. Effect of remote ischemic preconditioning on renal dysfunction after complex valvular heart surgery: a randomized controlled trial. *J Thorac Cardiovasc Surg* 2011;142:148–54.
23. Yang Y, Lang XB, Zhang P, *et al*. Remote ischemic preconditioning for prevention of acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2014;64:574–83.
24. Kanoria S, Jalan R, Seifalian AM, *et al*. Protocols and mechanisms for remote ischemic preconditioning: a novel method for reducing ischemia reperfusion injury. *Transplantation* 2007;84:445–58.
25. Aydin Z, van Zonneveld AJ, de Fijter JW, *et al*. New horizons in prevention and treatment of ischaemic injury to kidney transplants. *Nephrol Dial Transplant* 2007;22:342–6.
26. Veighey K, MacAllister R. Clinical applications of remote ischaemic preconditioning in native and transplant acute kidney injury. *Pediatr Nephrol* 2014. Published Online First: 4 Oct 2014. doi:10.1007/s00467-014-2965-6
27. Krogstrup NV, Soendergaard P, Secher NG, *et al*. Improved GFR and renal plasma perfusion following remote ischaemic conditioning in a porcine kidney transplantation model. *Transpl Int* 2012;25:1002–12.
28. Chen Y, Zheng H, Wang X, *et al*. Remote ischemic preconditioning fails to improve early renal function of patients undergoing living-donor renal transplantation: a randomized controlled trial. *Transplantation* 2013;95:e4–6.
29. Wu J, Feng X, Huang H, *et al*. Remote ischemic conditioning enhanced the early recovery of renal function in recipients after kidney transplantation: a randomized controlled trial. *J Surg Res* 2014;188:303–8.
30. REPAIR trial. http://repair.lshtm.ac.uk; http://www.isrctn.com/ISRCTN30083294
31. RIPNOD study. https://clinicaltrials.gov/ct2/show/study/NCT01515072
32. Remote Post-Conditioning (RPC) in renal transplantation. http://www.isrctn.com/ISRCTN66437627
33. Kottenberg E, Thielmann M, Bergmann L, *et al*. Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol—a clinical trial. *Acta Anaesthesiol Scand* 2012;56:30–8.
34. Belhomme D, Peynet J, Louzy M, *et al*. Evidence for preconditioning by isoflurane in coronary artery bypass graft surgery. *Circulation* 1999;100:II340–4.
35. Toller WG, Kersten JR, Pagel PS, *et al*. Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischemic preconditioning in dogs. *Anesthesiology* 1999;91:1437–46.
36. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. *Annu Rev Pharmacol Toxicol* 2008;48:463–93.
37. Kusaka M, Iwamatsu F, Kuroyanagi Y, *et al*. Serum neutrophil gelatinase associated lipocalin during the early postoperative period predicts the recovery of graft function after kidney transplantation from donors after cardiac death. *J Urol* 2012;187:2261–7.
38. Yamamoto T, Noiri E, Ono Y, *et al*. Renal L-type fatty acid—binding protein in acute ischemic injury. *J Am Soc Nephrol* 2007;18:2894–902.
39. Schmidt IM, Hall IE, Kale S, *et al*. Chitinase-like protein Brp-39/YKL-40 modulates the renal response to ischemic injury and predicts delayed allograft function. *J Am Soc Nephrol* 2013;24:309–19.

BMJ Open

Remote ischaemic conditioning on recipients of deceased renal transplants, effect on immediate and extended kidney graft function: a multicentre, randomised controlled trial protocol (CONTEXT)

Nicoline V Krogstrup, Mihai Oltean, Bo M Bibby, Gertrude J Nieuwenhuijs-Moeke, Frank J M F Dor, Henrik Birn and Bente Jespersen

BMJ Open 2015 5:
doi: 10.1136/bmjopen-2015-007941